REMARKS

Claims 1-43 are pending in the present application.

Claims 32, 39 to 42 have been amended. Support for these amendments can be found at page 12, line 8 - page 13, line 23. It is submitted that none of these amendments constitute new matter, and their entry is requested.

Rejection under 35 U.S.C. §112, second paragraph

On page 2, the Office rejects claims 40 and 41 under 35 USC §112, second paragraph as indefinite for lack of antecedent basis of the terms "the substituents" (claim 40) and "said targeting molecule" (claim 41).

In response, applicants have amended claims 40 and 41 to provide clear antecedent basis for the respective terms. Withdrawal of this rejection is requested.

Rejections under 35 U.S.C. §112, first paragraph, written description

On pages 2-4, the Office rejects claims 1-43 under 35 USC §112, first paragraph for lack of a written description. In particular, the Office alleges that the disclosure does not describe elements that are essential to the genus comprising covalently conjugated non-reactive atoms in bioactive agent molecules and the genus comprising an inactive form of a bioactive agent that is cleaved to an active form. On page 4, the Office also alleges that the specification fails to teach or adequately describe a representative number of species. The Office concludes that the inventors were not in possession of the claimed genera at the time the application was filed.

Applicants submit that the person skilled in the art would have, from the examples provided, recognized that the inventors were in possession of the claimed invention. In particular, the nature of the non-reactive atom is explained and examples are given on page 12 of the specification. It is submitted that the person skilled in the art would understand that the nature of the non-reactive atom is a function of the bioactive agent that is transported into a cell. Spacers are disclosed on pages 13-

14 of the specification. A representative number of examples for cleaving the bioconjugates of the present invention to release a bioactive agent are provided on pages 43-47 of the specification. Thus, Applicant's submit that the disclosure provides sufficient relevant identifying characteristics and /or examples that the person skilled in the art would recognize that the inventors were in possession of the claimed invention.

Applicants have amended claims 39, 40 and 42 to more clearly define the organocobalt complex as supported at pages 12-13 of the specification

In view of the above amendments and remarks, it is submitted that the claimed invention is fully described by the specification. Withdrawal of this rejection is requested.

Rejections under 35 U.S.C. §112, first paragraph, enablement

On pages 4-8, the Office rejects claims 1-43 under 35 USC §112, first paragraph for lack of enablement.

In particular, the Office contends that, while the specification is enabling for the *in vitro* delivery, sonolysis and photolysis of B_{12} and Co[SALEN] bioconjugates to target cells, it does not reasonably provide enablement for the targeting of any and/or all cells and tissue sites *in vivo*, and the subsequent cleavage via a self destructive linker.

State of the prior art/ predictability

The Office states that Quadros et al., Collins et al., and McEvans et al. illustrate that there exists a high level of unpredictability regarding the successful targeting, delivery and metabolism of organocobalt complexes (see page 5). The Office provides the following technical reasoning to fulfill the evidentiary standards set by *In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

(1) Targeting and delivery:

The Office seem to rely primarily on Collins et al. to support its contention of the unpredictability of cell targeting and delivery. In particular, the Office appears to allege that Collins et al.'s conclusion in the abstract that "further evaluation of cobalamine analogues and their

interaction with transport proteins and cellular receptors within malignant tissue and infection is warranted" as well as Collins et al. results that show enhanced cellular uptake in some malignant tissues compared with others supports that the targeting and delivery of the claimed bioconjugates/bioactive agents is unpredictable (a). The Office also appears to argue that the alleged teaching of various binding affinities of vitamin B_{12} for transcobalamin in McEvans et al. supports that the delivery of the claimed bioconjugates/bioactive agents is unpredictable (b).

(2) Metabolism:

To support unpredictability of metabolism, the Office cites Quadros et al. The Office appears to allege that Quadros et al.'s teaching that the intracellular events leading to the synthesis and subsequent disposition of certain cobalt forms are largely unknown supports that the metabolism of the claimed bioconjugates/bioactive agents is unpredictable (a). The Office also refers to the last paragraph on page 401 of Quadros et al. for an alleged teaching that the efflux of cobalt and cobalt complexes from target cells was not predictable (b). The Office also seeks to support its contention with McEvans et al.'s report of photolability of bonds with the Co metal center of vitamin B_{12} (c).

Applicants respectfully submit that the Office has not met its evidentiary burden under *In re Marzocchi*, 169 USPQ 367 (CCPA 1971) for the following reasons.

(1) Targeting/ Delivery:

(a) With regard to the Collins et al reference, applicants notes that this reference fully supports the *in vivo* uptake of cobalamin, in particular **modified** cobalamin, by human tumors (se pages 571 to 574). Thus, Collins et al. teach that gross changes to the cobalamin molecule are tolerated by the cobalamin transport system. Collins also support that highly proliferating tumors are good targets of their modified cobalamin. Applicants refer the Office to page 568, last two lines in the left column to 3rd line in the right column, as well as to page 577, left column, first four lines under the heading "Novel Radiolabeling of Adenosylcobalamin." Collins also provides an explanation as to why an enhanced cellular uptake occurs in some malignant tissues, but not in others, that was observed by the Office. See page 579, left column. Here the reference discusses

an observed correlation between the aggressiveness of a tumor and the amount of uptake of the vitamin B_{12} analog. Thus, Collins et al., at best, support that the bioconjugates/bioactive agents may be better suited for the treatment of aggressive tumors, rather than low grade tumors. Otherwise Collins fully supports enablement of the present invention.

(b) With regard to the McEvans reference, applicants, after careful review, cannot agree with the Office's interpretation of the last paragraph on page 1131 of the reference. The reference appears to teach that reported vitamin B_{12} derivatives largely retain their binding affinity for TCII. Applicants believe that the paragraph supports the successful uptake of the discussed derivatives. A further explanation of the Office's rationale would be appreciated.

An earlier reference having Collins and Hogenkamp as authors also supports that the *in vivo* uptake of modified cobalamin is enabled, namely, Collins, D.A.; Hogenkamp, H.P.C., "Transcobalamine II receptor Imagining via Radiolabled Diethylene-Triaminepentaacetate Cobalamin Analogs." *Nucl. Med. 38*, 717-723 (1997)). Yet an earlier reference that supports uptake of cobalamin *in vivo* is Flodh, H. "Accumulation of labelled Vitamine B-12 in some Transplanted Tumors." *Acta Radiol. Suppl. 284*, 55-60 (1968). Upon request, applicants will be happy to provide such earlier reference to the Office. Alternatively or additionally, Applicants will be happy to provide a declaration by one of the inventors attesting to the contents of these references.

(2) Metabolism:

(a) Firstly, applicants note that Quadros et al. teach the successful uptake of cobalamin into L-1210 cells. Additionally, the cobalamin forms cited by the Office and referred to on page 395 are specific intracellular cobalamin forms that serve as co-factors of two cobalamin dependent enzymes, namely a cytosolic methionine synthase (MS) and a mitrochonrial methylmalonyl-CoA mutase (MU). Quadros et al.'s comment that "the intracellular events leading to the synthesis and subsequent disposition" are largely unknown refers to these particular forms of cobalamin. Applicants submit that the synthesis and disposition of certain co-factor forms of cobalamin, even if they were largely unknown, would have little, if any, bearing on the disposition of the claimed

bioconjugates/bioactive agents. As reported by Collins, human tumors could be visualized with labeled cobalamin at 3 to 5 and 24 hours after injection, supporting relative good retention of Collin's modified cobalamin or at least the label attached to the cobalamin.

(b) With regard to the Office's interpretation of Quadros et al.'s statement in the last paragraph of page 401, applicants read this paragraph to only refer to an efflux of free cobalamin. Quadros et al. describes this efflux as a way of the cell to dispose of excess cobalamin that is not needed within the cell. Applicants submit that the fate of free cobalamin is not indicative of the fate of the bioconjugates or bioactive agents of the present invention; it certainly does not support that the fate of the bioconjugates or bioactive agents of the present invention is unpredictable. Whether the efflux of free cobalamin occurs only *in vitro* or also *in vivo* is not relevant.

(c) With regard to the Office's contention that the metabolism of the bioconjugates or bioactive agents of the present invention is unpredicatble, in view of McEvan's report of photolability of bonds with the Co metal center of vitamin B_{12}, applicants note that photochemical release of the bioactive agents is indeed desirable in te context of the present invention and a factor throughoutly considered by the inventors. See, e.g., page 44, lines 21-27. The reported photolability is not indicate of the unpredicatablity of the metabolism of the bioconjugates of the present invention.

In sum, Applicants submit that the Office has not met its evidentary burden to support that targeting, delivery and metabolism of the claimed bioconjugates is unpredictable.

Guidance

Applicants further submit that specification provides adequate guidance for the *in vivo* delivery and processing of the bioconjugates of the present invention. As the Office has acknowledges, a number of examples using cell lines are provided. See, e.g., Examples 3 and Examples 8 and 9. As far as the Office contention of lack of correlation between the *in vitro* and the *in vivo* data is concerned, Applicants submit that apart from the existence of working examples, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such

that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the Office has evidence that the model does not correlate. Even with such evidence, the Office must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. *In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)* (reversing the PTO decision based on finding that in vitro data did not support in vivo applications) (MPEP §2164.02). Applicants submit that, as evidenced by the discussion above, the state of the prior art is such that one skilled in the art would accept the *in vitro* models used as reasonably correlating to the *in vivo* events. In fact, the Office, by relying on Quadros et al, who uses murine cell lines rather than the human cell lines used by the inventors, appears to acknowledge the validity of such models.

Breadth of the Claims/Quantity of Experimentation required

In view of the discussion above, Applicants submit that the claims are not overly broad. Any experimentation that might be required to make and use the present invention is not undue in view of the state fo the prior art and the degree of guidance provided.

In view of the above amendments and remarks, it is submitted that the claimed invention is fully described and enabled by the specification. Withdrawal of this rejection is requested.

Claim Amendments

Any amendments to the claims were made solely for the purpose of clarifying the respective claim. In no case should such an amendment of an element of a claim be construed as a surrender of equivalents.

In view of the above amendments and remarks, in conjunction with the remarks made in the previous amendment, it is believed that the claims satisfy the requirements of the patent statutes and are patentable over the prior art. Reconsideration of the instant application and early notice of

allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

ROTHWELL, FIGG, ERNST & MANBECK, p.c.

By _____

Joyce von Natzmer
Registration No. 48,120
Attorney for Applicant
1425 K Street, N.W., Suite 800
Washington, D.C. 20005
phone: 202-783-6040
fax: 202-783-6031

L:\2317\PTOPAPER\107A.amend1.wpd